REMARKS

Introduction

Applicants have reproduced certain procedural notes as were presented in the June 5, 2009 Request for Reconsideration. Applicants' substantive remarks begin at page 10.

Procedural Remarks

Applicants concurrently filed a Declaration under 37 CFR 1.132 by a named co-inventor, Zoltán Gábor Tóth ("Declarant Toth"), of the present application.

Status of Claims

Claims 1-61 are pending. Claims 14, 27, and 60 are withdrawn from consideration. Claim 37 is amended in order to improve readability. Claims 62-65 are added. New claims 62 and 64-65 are directed to non-elected subject matter. Claim 63 is directed to elected subject matter. No new matter is believed to be added. Upon entry of the amendment, claims 1-13, 15-26, 28-59, and 63 are under consideration, while claims 14, 27, 60, 62, and 64-65 are withdrawn.

Information Disclosure Statement

Applicants thank the Examiner for pointing out the discrepancy concerning WO 02/42290 and WO 2004/042290 with regard to the Information Disclosure Statement filed 2 October 2008. Applicants filed a Letter dated 13 March 2009 explaining that WO 2004/042290 was listed in error and that WO 02/42290 is the reference that Applicants wish to consider. Applicants concurrently file an Information Disclosure Statement that cites WO 02/42290, as well as the Office Actions for related pending applications. Applicants kindly request that the Examiner consider this and the other references cited in the Information Disclosure Statement.

Withdrawn Rejections

Applicants note that the Examiner wrote in the Office Action dated 5 December 2008 at page 3 that "[r]ejections and/or objections not reiterated from the previous Office Action are hereby withdrawn." Applicants interpret this passage to mean that because the 5 December 2008 Office Action does not include a rejection under 35 U.S.C. § 103(a) over Schumacher (U.S. Patent No. 6,506,767) then this rejection has been formally withdrawn.[1] Clarification is requested.

[1] The claims had been previously rejected under 35 U.S.C. §103(a) over Schumacher in the 21 August 2006 Office Action (see pages 9ff) and in the 16 July 2007 Office Action (see page 6ff).

Claims Rejections – 35 U.S.C. § 102

The Office has taken the position that claims 1-13, 15-26, 28-59, and 61 are unpatentable under 35 U.S.C. §102(b) as being *inherently* anticipated by:

(1) Villani (U.S. Patent No. 4,659,716), as evidenced by Schumacher;

(2) Schumacher '855 (EP 0 208 855), as evidenced by Schumacher; and

(3) Piwinski (WO 92/002293) as evidenced by the arguments filed by Quimica Sintetica, S.A. in the Notice of Opposition to European Patent 1 507 531, and further evidenced by the Excerpt from the Opposition proceedings concerning EP 0 993455.

Applicants note that with respect to the outstanding issue, the subject matter of Villani is substantially the same as the subject matter of Schumacher '855. Thus, the rejection based on Schumacher '855 is redundant in view of the rejection based on Villani.[2] Applicants invite the Examiner to compare the relevant disclosure of Villani to the relevant disclosure of Schumacher '855. For convenience, Applicants have reproduced the text of these two documents below with the substantive differences underlined.[3]

Villani (U.S. 4,659,716)	Schumacher '855 (EP 0 208 855)
Col. 17, line 63 – col. 18, line 7 EXAMPLE V 8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine The acetic acid salt prepared as in Example II is dissolved in a minimum amount of water and the solution is made basic with a dilute aqueous solution of potassium carbonate. A pink colored oil separates. Extract the organic material with chloroform, wash with water and remove the solvent. Triturate the residue with hexane. Recrystallize from a large volume of hexane after charcoal decolorization to obtain the product, m.p. 151°-152°C.	Page 29 EXAMPLE V 8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine The acetic acid salt prepared in Example III is dissolved in a minimum amount of water and the solution is made basic with a dilute aqueous solution of potassium carbonate. A pink colored oil separates. Extract the organic material with chloroform, wash with water and remove the solvent. Triturate the residue with hexane. Recrystallize from a large volume of hexane after charcoal decolorization to obtain the product, m.p. 151-152°C.
Col. 18, ll. 34-51 B. 8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine. A solution of 14 grams of the N-cyano compound from part A in 60 mL of concentrated hydrochloric	Page 30 B. 8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine. A solution of 14 grams of the N-cyano compound from part A in 60 mL of concentrated hydrochloric

[2] Applicants note that Schumacher '855 claims priority to three U.S. non-provisional applications: (1) 06/733,428, filed 13 May 1985, (2) 06/838,974, filed 12 March 1986, and (3) 06/839,974, filed 12 March 1986. Incidentally, Villani issued from 06/838,974, filed 12 March 1986.

[3] Villani's reference to Example II is incorrect, while Schumacher '855's reference to Example III is correct.

Villani (U.S. 4,659,716)	Schumacher '855 (EP 0 208 855)
acid, 600 mL of glacial acetic acid and 400 mL of water is refluxed with stirring for 20 hours. The solvents are removed in vacuo and the residue dissolved in water and neutralized with ammonium hydroxide. The material is extracted several times with chloroform, the chloroform extracts washed with water and concentrated to dryness, and the residue triturated with petroleum ether or hexane to yield 11.5 grams (93%) m.p. 149°-151°C. After recrystallization from hexane, the product melts at 150°-151°C. Anal. Calcd. for $C_{19}H_{19}N_2Cl$: C,73.42; H,6.16; N,9.01. Found: C,73.19; H,6.14; N,8.91.	acid, 600 mL of glacial acetic acid and 400 mL of water is refluxed with stirring for 20 hours. The solvents are removed in vacuo and the residue dissolved in water and neutralized with ammonium hydroxide. The material is extracted several times with chloroform, the chloroform extracts washed with water and concentrated to dryness, and the residue triturated with petroleum ether or hexane to yield 11.5 grams (93%) m.p. 149-151°C. After recrystallization from hexane, the product melts at 150-151°C. Anal. Calcd. for $C_{19}H_{19}N_2C1$: C,73.42; H,6.16; N,9.01. Found: C,73.19; H,6.14; N,8.91.

Applicants believe that the disclosures of Villani, Schumacher '855 and Piwinski do not inherently anticipate the claims of the present application.

Villani and Schumacher '855

As to the above-noted passages, there are three instances in Villani, where solid desloratadine is formed.[4] Inspection of each three of these instances shows that Villani does not inherently anticipate the claimed compositions.

Applicants note that first instance where Villani provides solid desloratadine follows from the expression "...and remove the solvent" or "concentrated to dryness." See Villani at col. 18, lines 4 and 45-46.[5] The solvent in this example is chloroform.

Declarant Toth found that when a chloroform solution of desloratadine is concentrated to dryness, i.e., the solvent is removed, XRD shows that the resultant desloratadine is "form 2 with a trace of form 1." See Toth Declaration at p. 3, para. 15.

The second instance where solid desloratadine is realized in the passage above relates to the trituration step.

Declarant Toth found that after desloratadine is triturated with n-hexane, the resultant desloratadine is "form 2 with a trace of form 1." *Id.* at p. 3, para. 16.

The third instance where solid desloratadine is mentioned in Villani relates to the disclosure that recites: "Recrystallize from a large volume of hexane..."

Applicants note that Villani does not describe what the term "large" means. Notwithstanding Villani's deficient disclosure, Declarant Toth found that desloratadine is not soluble in a 200-fold excess of n-hexane at 45°C. See Toth Declaration at p. 4, para.

[4] The Villani Example at issue is written as a prophetic example.

[5] See also Schumacher '855 at 29-30.

23. Applicants believe that 200-fold excess of n-hexane is certainly a large amount of hexane. Declarant Toth found that desloratadine could be suspended in n-hexane. *Id.* at pp. 3-4, paras. 17-19 and 21. Declarant Toth also found that the polymorphic form in at least two instances did not change. *Id.* at pp. 3-4, paras. 18-19 and 21. Declarant Toth found that in one instance, see p. 3, para. 17, a mixture of form 1 and form 2 desloratadine was realized. However, in the other three instances only form 1 was realized.

Finally, Declarant Toth performed two experiments in order to obtain desloratadine from desloratadine acetate. *Id.* at p. 2, para. 12 and p. 3 at para. 14. In the first experiment (para. 12), the "sample presented polymorphic form 2 by XRD," while in the second experiment (para. 14), the "sample presented a mixture of form 1 (25%) and form 2 (75%) by XRD."

Inherent anticipation exists "if a single prior art reference discloses each and every limitation of the claimed invention," even though one of the limitations is inherently disclosed provided that the limitation "is necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). In *Schering*, the Federal Circuit found that claims 1 and 3 of U.S. Patent No. 4,659,716 (i.e., Villani!) that embrace desloratadine were inherently anticipated by the disclosure of U.S. Patent No. 4,282,233 ("the '233 patent"). The key aspect relied on the *Schering Court* was that the inherent limitation "is necessarily present…in the single anticipating reference." The *Schering Court* reasoned that although the '233 patent does not explicitly disclose desloratadine, the '233 patent discloses administering loratadine to a patient. The facts showed that when loratadine is administered to a patient desloratadine is necessarily formed. Because desloratadine is necessarily formed when administered to a patient, the '233 patent enabled one of ordinary skill how to make desloratadine, and thus, the '233 patent inherently anticipated claims 1 and 3 of Villani. Although claims 1 and 3 of Villani were found to be inherently anticipated by the '233 patent, Applicants believe that, in view of the Toth Declaration, Villani cannot be said to inherently anticipate the presently claimed compositions because Villani does not *necessarily* disclose polymorphic mixtures of desloratadine as presently claimed. Applicants also believe that this reasoning is equally applicable to Schumacher '855. In view of the above, Applicants respectfully request that the Examiner withdraw these two rejections.

Piwinski

Piwinski discloses preparing desloratadine by hydrolysis of loratadine. See Piwinski Example 1G at pp. 78-79. Piwinski discloses obtaining an intermediate desloratadine product by concentrating an ethyl acetate solution of desloratadine to dryness. Piwinski then discloses recrystallizing the intermediate desloratadine product from "toluene to give [a final desloratadine product] as a white solid." *Id.*

As to the intermediate desloratadine product, Applicants note that there is information of record showing that this intermediate product is not a mixture of polymorphic desloratadine.[6]

As to the final desloratadine product Applicants note that Piwinski does not disclose the exact procedure whereby desloratadine is recrystallized. For instance, Declarant Toth conducted three separate experiments by dissolving desloratadine in toluene to obtain a solution so as to obtain crystalline desloratadine from the solution. In the first experiment, "a mixture of form 1 (9%) and form 2 (91%)" was obtained. See Toth Declaration at pp. 1-2, para. 8. In two other experiments, only "form 2 (100%)" was obtained. *Id.* at p. 2, paras. 9-10. Applicants believe that Declarant Toth's experiments clearly show that Piwinski does not necessarily disclose a mixture of polymorphic desloratadine as presently claimed. Because Piwinski fails to necessarily provide an element of the claimed compositions, Applicants believe that it is improper to base inherent anticipation on the disclosure of Piwinski. Applicants believe that withdrawal of this rejection is warranted, and ask that the Examiner acknowledge the same.

On one final point, Applicants once again direct the Examiner's attention to Schering's 12 December 2006 Comments at page 7. In particular, Schering states that "two different mixtures of desloratadine with different ratios of polymorph Form 1 to polymorph Form 2 were subjected to dissolution in and crystallization from toluene, in accordance with the disclosure in Example 1G of [Piwinski]." *Id.* at p. 7, para. 3. As noted above, Piwinski does not disclose the exact procedure whereby desloratadine is recrystallized from toluene. However, Applicants ask that the Examiner consider Schering's allegation that "crystallization of desloratadine from toluene consistently results in a mixture of approximately 80% of polymorph Form 1 desloratadine and 20% of polymorph Form 2 desloratadine." *Id.* Applicants also ask that the Examiner compare Schering's allegation to the results found in the Toth Declaration, which clearly shows that the ratio of polymorphs appears to be related to the manner in which crystallization is conducted. Although it is unclear what crystallization procedure Schering used in "reproducing" Piwinski's Example 1G, what is clear is that the polymorphic ratio appears to depend on the crystallization process, and moreover, this information bolsters the notion that polymorphism is truly unpredictable.

No Issue of Obviousness over Villani or Piwinski

Although it permissible to base obviousness on an inherent disclosure,[7] Applicants believe that it would be improper to do so here because neither Villani nor Piwinski disclose that desloratadine exhibits polymorphism. Absent such a disclosure, one of ordinary skill would not know that a mixture of polymorphs would be possible. Of course, Schumacher discloses that desloratadine exhibits polymorphism, but

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[6] *See* Schering's 12 December 2006 Comments at page 5, pars. 1-2 made during the Opposition proceedings of EP 0 993 455 B1, which was considered by the Examiner Schlientz on November 26, 2008, but is attached herewith for convenience.

[7] *In re Napier*, 55 F.3d 610 (Fed. Cir. 1995).

Applicants believe, as presented below, that it is improper to base obviousness on Schumacher's disclosure.

Schumacher Revisited

Applicants requested above that the Examiner confirm that the outstanding rejection based on Schumacher (U.S. Patent No. 6,506,767) has been withdrawn. For the sake of completeness and convenience, Applicants have represented previous remarks provided in support of the patentability of the claimed compositions over Schumacher.

The claimed ranges for the polymorphic mixtures do not "overlap" or "touch" with the polymorphic mixture ranges disclosed in Schumacher. In fact, Schumacher instructs the public that it is undesirable to use desloratadine polymorphic mixtures in pharmaceutical compositions. For instance, Schumacher discloses that the polymorphic purity of desloratadine should be prepared in "as pure a form as possible," so as to have "constant physical properties," in order to meet the stringent requirements for FDA regulatory approval. *See* Schumacher at column 1, lines 34-41. A fair reading of Schumacher shows that a reason for achieving a certain polymorphic purity for desloratadine is because "a mixture [of polymorphs] could lead to production of a [desloratadine] product which would exist as a variable mixture of variable composition (i.e., variable percent amounts of polymorphs) having variable physical properties, a situation unacceptable in view of stringent GMP requirements." *Id.* at column 4, lines 5-11. In other words, Schumacher discloses that desloratadine having the highest possible polymorphic purity, i.e., a single polymorph, is to be preferred over a mixture of polymorphs since the former, having "constant physical properties," is perceived to be more likely to meet FDA Regulatory requirements. Taken this information together, it should be clear that Schumacher teaches away from the presently claimed composition. Applicants also ask that the Office consider the fact that Applicants have discovered unexpectedly, and to the contrary of Schumacher's disclosure, that the presently claimed desloratadine compositions are quite **stable**. *See, e.g.*, Applicants' disclosure at page 13, line 29 – page 14, line 26, which discloses, in part, that the claimed desloratadine compositions / mixtures are **both chemically and polymorphically stable** under certain conditions. For example, Applicants disclose that "[t]he stable mixtures of 25:75, 50:50, 75:25, 84:16 (Form 1:Form 2) do not show any substantial change (Chemical: by degradation; Physical: by transformation to another polymorphic form) in the XRD pattern after exposure at 60%, 80%, 100% RH for one week." *Id.* The fact that Applicants discovered that the presently claimed desloratadine polymorphic mixtures are stable under these conditions is most unexpected in view of the disclosure of Schumacher. For at least the reasons provided above, Applicants believe that the claimed subject matter is unobvious over Schumacher.

Double Patenting

Applicants previously requested that the provisional obviousness-type double patenting rejection of claims 1-3, 15-26, 28-59, and 61 over claims 21-24 of 11/283,276 be held in abeyance until there is an indication of allowable subject matter in the present

application. Applicants firmly believe that the present application is now in a condition for allowance, and based on the guidelines Applicants believe that this provisional rejection should be withdrawn. See **MPEP 804.I.B**. Applicants respectfully request that the Examiner acknowledge the same and withdraw this rejection.

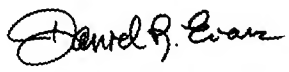
Rejoinder Requested

Claims 14, 27, 60, 62, and 64-65 are withdrawn. Applicants believe that the claims on which these withdrawn claims depend are now in a condition for allowance. Thus, Applicants respectfully request that the Examiner rejoin these withdrawn claims. See **MPEP 821.04**.

In view of the remarks contained herein, Applicants respectfully request a Notice of Allowance. If the Examiner believes that a discussion would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

23552
PATENT TRADEMARK OFFICE

Respectfully submitted,
MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(404) 954-5061



Daniel R. Evans, Ph.D.
Registration No. 55,868

Date: **July 6, 2009**

LEXSEE 339 F.3D 1373

SCHERING CORPORATION, Plaintiff-Appellant, v. GENEVA PHARMACEUTICALS, INC. and NOVARTIS CORPORATION, and TEVA PHARMACEUTICALS USA, INC., and ANDRX CORPORATION, ANDRX PHARMACEUTICALS LLC, and ANDRX PHARMACEUTICALS, INC., and MYLAN PHARMACEUTICALS, INC., and WYETH, ESI-LEDERLE, WYETH PHARMACEUTICALS, and WYETH CONSUMER HEALTHCARE (formerly American Home Products Corporation, Wyeth-Ayerst Laboratories, and Whitehall Robbins Healthcare), and IMPAX LABORATORIES, INC., APOTEX, INC. and NOVEX PHARMA, COPLEY PHARMACEUTICAL, INC., and GENPHARM, INC., Defendants-Appellees.

02-1540, 02-1541, 02-1542, 02-1543, 02-1544, 02-1545, 02-1546, 02-1547, 02-1548, 02-1549, 03-1021, 03-1022, 03-1023, 03-1025, 03-1027

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

339 F.3d 1373; 2003 U.S. App. LEXIS 15496; 67 U.S.P.Q.2D (BNA) 1664

August 1, 2003, Decided

SUBSEQUENT HISTORY: Rehearing denied by, Rehearing, en banc, denied by Schering Corp. v. Geneva Pharms., Inc., 348 F.3d 992, 2003 U.S. App. LEXIS 22046 (Fed. Cir., Oct. 28, 2003)

PRIOR HISTORY: [**1] Appealed from: United States District Court for the District of New Jersey. Chief Judge John W. Bissell.
Schering Corp. v. Geneva Pharms., Inc., 275 F. Supp. 2d 534, 2002 U.S. Dist. LEXIS 14587 (D.N.J., 2002)

DISPOSITION: Affirmed.

COUNSEL: Robert G. Krupka, Kirkland & Ellis, of Los Angeles California, argued for plaintiff-appellant. Of counsel on the brief were David P. Swenson, Kirkland & Ellis, of Washington, DC; John M. Desmarais, Sandra A. Bresnick, Peter J. Armenio, Maxine Y. Graham, Monica V. Bhattacharyya, and Young J. Park, Kirkland & Ellis, of New York, New York. Of counsel were John F. Hoffman and Arthur Mann, Schering Corporation, of Kenilworth, New Jersey.

Robert D. Bajefsky, Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., of Washington, DC, argued for defendants-appellees Wyeth, ESI-Lederle, Wyeth Pharmaceuticals and Wyeth Consumer Healthcare (formerly American Home Products Corporation, Wyeth-Ayerst Laboratories, and Whitehall Robbins Healthcare). With him on the brief were Barbara R. Rudolph and Matthew J. Mason. Of counsel on the brief were David A. Manspeizer and Lawrence Alaburda, WYETH, of Madison, New Jersey. On the brief was Julie A. Petruzzelli, Venable, Baetjer, Howard, & Civiletti, LLP, of Washington, DC, for defendant-appellee Impax Laboratories, Inc. Of counsel were Peter [**2] J. Curtin and James E. Gray. Also on the brief were Edgar H. Haug, Daniel G. Brown, and Porter F. Fleming, Frommer Lawrence & Haug LLP, of New York, New York; for defendant-appellee Genpharm Inc.; Colin A. Underwood, Soloman, Zauderer, Ellenhorn, Frischer & Sharp, of New York, New York, for defendants-appellees Andrx Corporation, Andrx Pharmaceuticals LLC, and Andrx Pharmaceuticals, Inc.; E. Anthony Figg, Joseph A. Hynds, Rothwell, Figg, Ernst & Manbeck, of Washington, DC, for defendant-appellee Mylan Pharmaceuticals, Inc.

Robert S. Silver and William J. Castillo, Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd., of Philadelphia, Pennsylvania for defendants-appellees Apotex, Inc. and Novex Pharma.

Thomas L. Creel, Goodwin Procter, LLP, of New York, New York, for defendants-appellees Teva Pharmaceuticals USA, Inc. and Copely Pharmaceutical, Inc. With him on the brief were Frederick H. Rein and Keith A. Zullow.

Douglass C. Hochstetler, Schiff, Hardin & Waite, of Chicago, Illinois, argued for defendants-appellees Geneva Pharmaceuticals, Inc. and Novartis Corporation.

With him on the brief were Patricia J. Thompson and Jo-Anne M. Kokoski. Of counsel on the brief was Kevin [**3] M. Flowers, Ph.D., Marshall Gerstein & Borun, of Chicago, Illinois.

JUDGES: Before RADER, Circuit Judge, PLAGER, Senior Circuit Judge, and BRYSON, Circuit Judge.

OPINION BY: RADER

OPINION

[*1374] RADER, *Circuit Judge.*

On summary judgment, the United States District Court for the District of New Jersey determined that claims 1 and 3 of U.S. Patent No. 4,659,716 (the '716 patent) are invalid. *Schering Corp. v. Geneva Pharm., Inc.*, 275 F. Supp. 2d 534, 2002 U.S. Dist. LEXIS 14587, No. 98-1259 (D.N.J. Aug. 8, 2002). Because the district court correctly found that U.S. Patent No. 4,282,233 (the '233 patent) inherently anticipates claims 1 and 3 of the '716 patent, this court affirms.

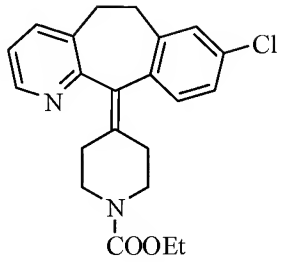
[*1375] I.

Schering Corporation (Schering) owns the '233 and '716 patents on antihistamines. Antihistamines inhibit the histamines that cause allergic symptoms.

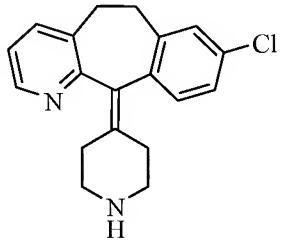
The prior art '233 patent covers the antihistamine loratadine, the active component of a pharmaceutical that Schering markets as CLARITIN TM. Unlike conventional antihistamines when CLARITIN TM was launched, loratadine does not cause drowsiness.

The more recent '716 patent at issue in this case covers a metabolite of loratadine called descarboethoxy-loratadine (DCL). A metabolite is the compound formed in the [**4] patient's body upon ingestion of a pharmaceutical. The ingested pharmaceutical undergoes a chemical conversion in the digestion process to form a new metabolite compound. The metabolite DCL is also a non-drowsy antihistamine. The '716 patent issued in April 1987 and will expire in April 2004 (the '233 patent issued in 1981 and has since expired). *See* 35 U.S.C. § 154(c)(1) (2000) (defining the term of a patent in force before June 8, 1995, as the greater of twenty years from the earliest U.S. priority date or seventeen years from grant).

Structurally, loratadine and its metabolite DCL differ only in that loratadine has a carboethoxy group (i.e., -COOEt) on a ring nitrogen, while DCL has a hydrogen atom on that ring nitrogen:



Loratadine

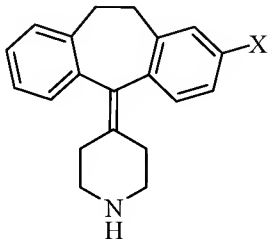


metabolite DCL

Loratadine ('233 patent) DCL ('716 patent)

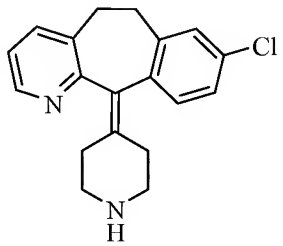
Claim 1 of the '716 patent covers DCL (for X = Cl), its fluorine analog, and their salts; claim 3 covers only DCL and its salts:

1. A compound of the formula



[*1376] or a pharmaceutically acceptable salt thereof, wherein X represents Cl or F.

3. A compound having the structural formula



[**5] or a pharmaceutically acceptable salt thereof.

The '233 patent issued on August 4, 1981, over one year before the earliest priority date of the '716 patent, February 15, 1984. The '233 patent is thus prior art to the

'716 patent. *See* 35 U.S.C. § 102(b) (2000) ("A person shall be entitled to a patent unless . . . the invention was patented . . . in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States."). The '233 patent discloses a class of compounds including loratadine (disclosed in Example 1B). '233 patent, col. 3, ll. 5-12. The '233 patent claims loratadine in claim 7. *Id.*, col. 6, ll. 38-40. The '233 patent claims four other compounds in claims 8-11. Examples 6-7 are prophetic[1] examples of pharmaceutical compositions (a syrup and a tablet), each containing an unidentified "active compound." The '233 patent does not expressly disclose DCL and does not refer to metabolites of loratadine.

1 Prophetic examples are set forth in the present tense to indicate that they were not carried out. *Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1578 (Fed. Cir. 1984).

[**6] The numerous defendants-appellees sought to market generic versions of loratadine once the '233 patent expired. Seeking regulatory approval, each appellee submitted an application to the Food and Drug Administration (FDA). *See* 21 U.S.C. § 355(b), (j) (2000). Because Schering included the '716 patent in the Orange Book listing for loratadine, the applications also contained a certification that the '716 patent was invalid. *See id.* § 355(b)(2)(A), 355(j)(2)(A)(vii). The appellees notified Schering of the FDA filings. *See id.* § 355(b)(3)(B), 355(j)(2)(B)(ii).

After receiving notice of the FDA filings, Schering filed suit for infringement. *See* 35 U.S.C. § 271(e)(2)(A) (2000). After discovery, the parties filed cross motions for summary judgment on the validity issue. The district court construed claims 1 and 3 of the '716 patent to cover DCL in all its forms, including "metabolized within the human body" and "synthetically produced in a purified and isolated form." The parties agreed to that construction. Applying that claim construction, the district court found that the '233 patent did not expressly disclose DCL. Nonetheless, [**7] the district court also found that DCL was necessarily formed as a metabolite by carrying out the process disclosed in the '233 patent. The district court concluded that the '233 patent anticipated claims 1 and 3 of the '716 patent under 35 U.S.C. § 102(b). The district court therefore granted the appellees' motions for summary judgment of invalidity. Schering timely appealed to this court under 28 U.S.C. § 1295(a)(1) (2000).

II.

This court reviews a grant of summary judgment without deference. *Telemac Cellular Corp. v. Topp Telecom, Inc.*, [*1377] 247 F.3d 1316, 1323 (Fed. Cir. 2001). In reviewing a summary judgment determination, this court draws all reasonable inferences in favor of the non-movant. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255, 91 L. Ed. 2d 202, 106 S. Ct. 2505 (1986).

A.

A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. *Lewmar Marine, Inc. v. Barient, Inc.*, 827 F.2d 744, 747 (Fed. Cir. 1987). Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention [**8] if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991).

At the outset, this court rejects the contention that inherent anticipation requires recognition in the prior art. Schering relies on *Elan Pharmaceuticals, Inc. v. Mayo Foundation for Medical Education & Research*, 304 F.3d 1221 (Fed. Cir. 2002) for that proposition. This court has since vacated *Elan*. *See* 314 F.3d 1299 (Fed. Cir. 2002). Other precedents of this court have held that inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. *E.g.*, *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1351 (Fed. Cir. 2002); *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999) ("Where . . . the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results."); *Atlas Powder*, 190 F.3d at 1348-49 ("Because 'sufficient aeration' [**9] was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention. . . . An inherent structure, composition, or function is not necessarily known."). Thus, recognition by a person of ordinary skill in the art before the critical date of the '716 patent is not required to show anticipation by inherency. The district court therefore did not err in allowing for later recognition of the inherent characteristics of the prior art '233 patent.

Contrary to Schering's contention, *Continental Can* does not stand for the proposition that an inherent feature of a prior art reference must be perceived as such by a person of ordinary skill in the art before the critical date. In *Continental Can*, this court vacated summary judgment of anticipation of claims reciting a plastic bottle with hollow ribs over a prior art reference disclosing a plastic bottle. The record contained conflicting expert testimony about whether the ribs of the prior art plastic bottle were solid. The accused infringer's expert testified that the prior art plastic bottle was made by blow molding, a process that would inherently produce hollow ribs. The patentee's [**10] experts testified that the prior art plastic bottle had solid ribs. The patentee disputed

whether the blow molding inherently produced hollow ribs. Given the disputed material fact, this court vacated the summary judgment as improper. *Continental Can*, 948 F.2d at 1269. *Continental Can* makes no reference to whether the inherent feature, hollow ribs, was recognized before or after the critical date of the patent at issue. Read in context, *Continental Can* stands for the proposition that inherency, like anticipation itself, requires a determination of the meaning of the prior art. Thus, a court may consult artisans of ordinary skill to ascertain their understanding about subject matter disclosed by the prior art, including features inherent in the prior art. A court may resolve factual questions about the subject matter in the prior art by examining the reference through the eyes of a person of ordinary skill in the [*1378] art, among other sources of evidence about the meaning of the prior art. Thus, in *Continental Can*, this court did not require past recognition of the inherent feature, but only allowed recourse to opinions of skilled artisans to determine the scope [**11] of the prior art reference.

Cases dealing with "accidental, unwitting, and unappreciated" anticipation also do not show that inherency requires recognition. *See Eibel Process Co. v. Minn. & Ontario Paper Co.*, 261 U.S. 45, 67 L. Ed. 523, 43 S. Ct. 322, 1923 Dec. Comm'r Pat. 623 (1923); *Tilghman v. Proctor*, 102 U.S. 707, 26 L. Ed. 279, 1881 Dec. Comm'r Pat. 163 (1880). In contrast to the present case, the record in *Eibel* and *Tilghman* did not show that the prior art produced the claimed subject matter. The patent at issue in *Tilghman* claimed a method of forming free fatty acids and glycerine by heating fats with water at high pressure. In *Tilghman*, the record did not show conclusively that the claimed process occurred in the prior art. In reviewing the prior art, the Court referred hypothetically to possible disclosure of the claimed process. For example, the Court stated "we do not regard the accidental formation of fat acid in Perkins's steam cylinder . . . (if the scum which rose on the water issuing from the ejection pipe was fat acid) as of any consequence in this inquiry." *Tilghman*, 102 U.S. at 711. In *Eibel*, the Court found no evidence of the claimed subject matter [**12] in the prior art. *Eibel*, 261 U.S. at 66 ("We find no evidence that any pitch of the wire . . . had brought about such a result . . . and . . . if it had done so under unusual conditions, accidental results, not intended and not appreciated, do not constitute anticipation.").

Applying an inherency principle in the context of an on sale bar under 35 U.S.C. § 102(b), this court has distinguished *Eibel* and *Tilghman*. *See Abbott Lab. v. Geneva Pharms., Inc.*, 182 F.3d 1315, 1319 (Fed. Cir. 1999) ("If a product that is offered for sale inherently possesses each of the limitations of the claims, then the invention is on sale, whether or not the parties to the transaction recognize that the product possesses the claimed characteristics."); *Scaltech, Inc. v. Retec/Tetra, LLC*, 269 F.3d 1321, 1330 (Fed. Cir. 2001) ("Appreciation of the invention is not a requirement to trigger the statutory [on sale] bar."). In those cases, the product sold or offered for sale had an inherent, but unrecognized, feature that was a limitation of the asserted claims. *Id.* Thus, this court has distinguished *Eibel* and *Tilghman* [**13] , which therefore do not bind this court to find no anticipation because skilled artisans did not recognize that the prior art '233 patent inherently produced the claimed invention, DCL.

In the context of accidental anticipation, DCL is not formed accidentally or under unusual conditions when loratadine is ingested. The record shows that DCL necessarily and inevitably forms from loratadine under normal conditions. DCL is a necessary consequence of administering loratadine to patients. The record also shows that DCL provides a useful result, because it serves as an active non-drowsy antihistamine. In sum, this court's precedent does not require a skilled artisan to recognize the inherent characteristic in the prior art that anticipates the claimed invention.

B.

This court recognizes that this may be a case of first impression, because the prior art supplies no express description of any part of the claimed subject matter. The prior art '233 patent does not disclose any compound that is identifiable as DCL. In this court's prior inherency cases, a single prior art reference generally contained an incomplete description of the anticipatory subject matter, i.e., a partial description [**14] missing certain aspects. Inherency [*1379] supplied the missing aspect of the description. Upon proof that the missing description is inherent in the prior art, that single prior art reference placed the claimed subject matter in the public domain. This case does not present the issue of a missing feature of the claimed invention. Rather, the new structure in this case, DCL, is not described by the prior '233 patent.

Patent law nonetheless establishes that a prior art reference which expressly or inherently contains each and every limitation of the claimed subject matter anticipates and invalidates. *See, e.g., EMI Group N. Am., Inc., v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1350 (Fed. Cir. 2001) ("A prior art reference anticipates a patent claim if the reference discloses, either expressly or inherently, all of the limitations of the claim."); *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."). In these prior cases, however, inherency was only necessary [**15] to supply a single missing limitation that was not expressly disclosed in the prior

art. This case, as explained before, asks this court to find anticipation when the entire structure of the claimed subject matter is inherent in the prior art.

Because inherency places subject matter in the public domain as well as an express disclosure, the inherent disclosure of the entire claimed subject matter anticipates as well as inherent disclosure of a single feature of the claimed subject matter. The extent of the inherent disclosure does not limit its anticipatory effect. In general, a limitation or the entire invention is inherent and in the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art. *See Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001); *see also In re Kratz*, 592 F.2d 1169, 1174 (CCPA 1979) (suggesting inherent anticipation of a compound even though the compound's existence was not known).

In reaching this conclusion, this court is aware of *In re Seaborg*, 51 C.C.P.A. 1109, 328 F.2d 996, 1964 Dec. Comm'r Pat. 462 (CCPA 1964). In that case, this court's predecessor considered claims drawn [**16] to an isotope of americium made by nuclear reaction in light of a prior art patent disclosing a similar nuclear reaction process but with no disclosure of the claimed isotope. The court reversed a United States Patent and Trademark Office rejection of the claims for lack of novelty. This court's predecessor found that the prior art process did not anticipate the claims because the process would have produced at most one billionth of a gram of the isotope in forty tons of radioactive material, i.e., the isotope would have been undetectable. *Id.* at 998-99 ("The claimed product, if it was produced in the Fermi process, was produced in such minuscule amounts and under such conditions that its presence was undetectable."). In this case, DCL forms in readily detectable amounts as shown by the extensive record evidence of testing done on humans to verify the formation of DCL upon ingestion of loratadine.

This court sees no reason to modify the general rule for inherent anticipation in a case where inherency supplies the entire anticipatory subject matter. The patent law principle "that which would literally infringe if later in time anticipates if earlier," *Bristol- Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1378 (Fed. Cir. 2001), [**17] bolsters this conclusion. Similarly, "if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated." *Atlas Powder*, 190 F.3d at 1346. "The [*1380] public remains free to make, use, or sell prior art compositions or processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which allow them to operate. The doctrine of anticipation by inherency, among other doctrines, enforces that basic principle." *Id.* at 1348. Thus, inherency operates to anticipate entire inventions as well as single limitations within an invention.

Turning to this case, the use of loratadine would infringe claims 1 and 3 of the '716 patent covering the metabolite DCL. This court has recognized that a person may infringe a claim to a metabolite if the person ingests a compound that metabolizes to form the metabolite. *See Hoechst-Roussel Pharms., Inc. v. Lehman*, 109 F.3d 756, 759 (Fed. Cir. 1997) ("The right to exclude may arise from the fact that when administered, [the accused product] metabolizes into another product [**18] . . . which Hoechst has claimed."); *see also Zenith Lab., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1421-22 (Fed. Cir. 1994) (stating that a compound claim could cover a compound formed upon ingestion). An identical metabolite must then anticipate if earlier in time than the claimed compound.

The record shows that the metabolite of the prior art loratadine is the same compound as the claimed invention. Claims 1 and 3 are compound claims in which individual compounds are claimed in the alternative in Markush format. DCL is within the scope of claims 1 and 3. Because the prior art metabolite inherently disclosed DCL, claims 1 and 3 are anticipated and invalid. In other words, the record shows that a patient ingesting loratadine would necessarily metabolize that compound to DCL. That later act would thus infringe claims 1 and 3. Thus, a prior art reference showing administration of loratadine to a patient anticipates claims 1 and 3.

C.

This court next examines whether Schering's secret tests of loratadine before the critical date placed DCL in the public domain. Before the critical date, Schering only tested loratadine in secret. Thus, according to Schering, [**19] "DCL was not publicly used, or described in any printed publication, until after February 15, 1983, the critical date for the '716 patent under 35 U.S.C. § 102(b)." Schering thus argues that DCL did not "exist" in the public domain such that DCL could be prior art against the '716 patent.

Anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985). Thus, actual administration of loratadine to patients before the critical date of the '716 patent is irrelevant. The '233 patent suffices as an anticipatory prior art reference if it discloses in an enabling manner the administration of loratadine to patients.

Thus, this court examines whether the '233 patent contains an enabling disclosure of DCL. A reference may enable one of skill in the art to make and use a com-

pound even if the author or inventor did not actually make or reduce to practice that subject matter. *Bristol-Myers*, 246 F.3d at 1379; *see also In re Donohue*, 766 F.2d at 533 (sustaining an anticipation rejection [**20] over a reference disclosing a compound and other references disclosing sufficient information to make that compound). Indeed, information arising after the critical date may show that the claimed subject matter, as disclosed in a prior art reference, "was in the public's possession." *Bristol-Myers*, 246 F.3d at 1379 (citing *In re Donohue*, 766 F.2d at 534).

[*1381] An anticipatory reference need only enable subject matter that falls within the scope of the claims at issue, nothing more. To qualify as an enabled reference, the '233 patent need not describe how to make DCL in its isolated form. The '233 patent need only describe how to make DCL in any form encompassed by a compound claim covering DCL, e.g., DCL as a metabolite in a patient's body. The '233 patent discloses administering loratadine to a patient. A person of ordinary skill in the art could practice the '233 patent without undue experimentation. The inherent result of administering loratadine to a patient is the formation of DCL. The '233 patent thus provides an enabling disclosure for making DCL.

D.

Finally, this court's conclusion on inherent anticipation in this case does not preclude patent [**21] protection for metabolites of known drugs. With proper claiming, patent protection is available for metabolites of known drugs. *Cf. In re Kratz*, 592 F.2d 1169, 1174 (CCPA 1979) (stating that a naturally occurring strawberry constituent compound does not anticipate claims to the substantially pure compound); *In re Bergstrom*, 57 C.C.P.A. 1240, 427 F.2d 1394, 1401-02 (CCPA 1970) (stating that a material occurring in nature in less pure form does not anticipate claims to the pure material).

But those metabolites may not receive protection via compound claims. In this case, for instance, claims 1 and 3 broadly encompass compounds defined by structure only. Such bare compound claims include within their scope the recited compounds as chemical species in any surroundings, including within the human body as metabolites of a drug. As this case holds, these broad compound claims are inherently anticipated by a prior art disclosure of a drug that metabolizes into the claimed compound.

A skilled patent drafter, however, might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and [**22] isolated form, as in *Kratz* and *Bergstrom*, or as a pharmaceutical composition (e.g., with a pharmaceutically acceptable carrier). The patent drafter could also claim a method of administering the metabolite or the corresponding pharmaceutical composition. The '233 patent would not provide an enabling disclosure to anticipate such claims because, for instance, the '233 patent does not disclose isolation of DCL.

The '716 patent contains claims 5-13 covering pharmaceutical compositions and claims 14-16 covering methods of treating allergic reactions by administering compounds that include DCL. These claims were not found anticipated by the '233 patent.

III.

The district court found that "there is no genuine issue that the consumption of loratadine by humans, with a wide variety of health statuses, necessarily results in the natural production in the human body of the DCL metabolite." This court must also examine the record for any genuine issue of material fact about whether ingestion of loratadine necessarily produces DCL. The record does, for instance, contain expert testimony, including a proposed metabolic scheme and animal data, that questions whether ingestion of loratadine [**23] always forms DCL.

A dispute about a material fact is genuine "if the evidence is such that a reasonable jury could return a verdict for the nonmoving party." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248, 91 L. Ed. 2d 202, 106 S. Ct. 2505 (1986). In this case, the evidence supporting the district court's [*1382] conclusion is extensive. In thirteen clinical studies that Schering ran before May 1, 1987, all 144 patients involved had measurable amounts of DCL in their systems after ingesting loratadine. The district court found "no reports in any of the studies of any individual who did not metabolically produce DCL following the administration of loratadine." The appellees reported twenty-one clinical studies in which loratadine was administered to a total of 864 patients, all of whom formed measurable amounts of DCL in their systems. In addition, the record shows that since 1985 Schering's technical articles and Securities and Exchange Commission filings referred to DCL as the metabolite of loratadine. Also the Food and Drug Administration, the corresponding European agency, the Physician's Desk Reference, and Schering's CLARITIN TM package insert referred to DCL as [**24] the major metabolite of loratadine.

The record presents no data on humans to show that a genuine factual dispute exists about the formation of DCL after ingesting loratadine. Indeed Schering's own expert testified that no human has been found that does not metabolize loratadine to DCL, and that "there is no scientific data in the published literature that says that DCL is not formed from loratadine in humans." Based on

this record, no reasonable jury could find that DCL is not produced when a human ingests loratadine. This court therefore discerns no genuine issue of material fact.

CONCLUSION

The district court did not err in finding that the '233 patent discloses administering loratadine to a patient, and that DCL forms as a natural result of that administration. The district court correctly concluded that DCL is inherent in the prior art. Without any genuine issues of material fact, the district court correctly granted summary judgment that claims 1 and 3 are invalid as anticipated by the '233 patent.

COSTS

Each party shall bear its own costs.

AFFIRMED

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Dear Sirs

European Patent No. 0 993 455 B1
(European Patent Application No. 98932930.5)
"Polymorphs of 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo [5,6] cyclohepta [1,2-b] pyridine"
SCHERING CORPORATION

We refer to the Summons to Attend Oral Proceedings dated 28 August 2006. These are Patentee's submissions in preparation for the Oral Proceedings on 12 February 2007. They are filed in accordance with the provisions of Rule 71(a) EPC.

1. Interpretation and Attendance at the Oral Proceedings

Patentee hereby confirms that it will speak in English at the Oral Proceedings and repeats its earlier request for simultaneous interpretation into English from any other language.

The undersigned professional representative of the Patentee will be accompanied at the Oral Proceedings by Ms. Lisa Jakob and Mr. Henry Hadad, both of whom are US patent attorneys of Schering Corporation. The representative will also be accompanied by two technical experts, namely Mr. Caesar Snodgrass-Pilla and Dr. George Wu. Mr. Snodgrass-Pilla is the Associate Director of the Physical Chemical Characterization & Analysis Department of Schering-Plough Research Institute and Dr. Wu is a Distinguished Fellow of the Synthetic Chemistry Chemical & Physical Sciences Department of Schering-Plough Research Institute. A copy of the *curriculum vitae* of each technical expert is enclosed. We hereby request that both of the technical experts be allowed to speak directly to the Opposition Division (herein the "OD") in connection with the technology that is the subject of the patent in suit, and the disclosure in the cited documents D1 to D4. More particularly, the two technical experts will be able to provide evidence, to the extent that the OD considers it to be necessary, on the state of the art at the priority date of the patent in suit, including the skilled person's interpretation of the disclosure in document D1, and the identity of the products that may be produced when Example 1G of the document is conducted. The two technical experts will also be able to provide evidence on the analytical methods that may be used to identify the polymorphic forms of a crystalline substance and to interpret the infrared (IR) and X-ray diffraction spectra that Patentee filed on 8 November 2004, as well as the spectra that are filed herewith.

2. *The two products of Example 1G of document D1 (WO 92/00293)*

In connection with the requirements of Article 54 EPC, the Opponent has alleged that the subject matter that is defined by granted Claims 8-13 of the patent in suit lacks novelty over the disclosure in document D1. In this regard, the Opponent has asserted that the conduct of Example 1G of that document, which describes a process for producing desloratadine, inevitably leads to a crystalline product which is the polymorph Form 2 of desloratadine. In response to this assertion, the OD has reviewed the disclosure in document D1, and has suggested in its preliminary opinion accompanying the Summons to Attend Oral Proceedings that Example 1G in fact discloses two solid products whose identities are contested (see e.g. paragraph 4.3 on page 7 of EPO Form 2906). These two solid products are: (i) the product that is obtained after the extraction with ethyl acetate and the removal of organic solvent (herein referred to as the "intermediate product"); and (ii) the product that results from the process of crystallising the intermediate product from toluene (herein referred to as the "final product").

In this regard, Patentee has already submitted experimental evidence to show that *neither* of these two solid products is crystalline polymorph Form 2 desloratadine (in response to which the Opponent has failed to file a reply). Moreover, by means of the present submissions, the Patentee provides yet further evidence in support of this position (thereby responding to the invitation that was extended to both the Patentee and the Opponent in paragraph 4.6 of the OD's preliminary opinion; see page 10 of EPO Form 2906).

In light of the additional evidence and analysis that is provided herewith, together with the analysis and evidence that is already on file, Patentee respectfully submits that an assertion of lack of novelty over the disclosure in document D1 (or indeed an assertion of obviousness) simply cannot be maintained. There is no direct and unambiguous disclosure of the subject matter that is defined by Patentee's Claims 8-13, which relates to crystalline polymorph Form 2 desloratadine substantially free of polymorph Form 1, and any allegation to the contrary is clearly unjustified.

3. *The burden of proof versus the speculation by the Opponent*

Patentee maintains that the Opponent's allegations are entirely unjustified. They cannot be accepted for both legal and scientific reasons. As to the legal reasons, it will of course be readily understood by the OD that the Opponent bears the burden of proof of demonstrating that either the intermediate product or the final product of Example 1G is polymorph Form 2 desloratadine. However, that burden of proof has certainly not been discharged. Instead, the Opponent would seem to believe that it is sufficient to *simply speculate* that the solids of that example are the crystalline polymorph Form 2 desloratadine, *without providing any scientific evidence whatsoever to substantiate this allegation*. Of course, such speculation cannot be accepted since for the purposes of demonstrating that a lack of novelty exists, there must be more than mere speculation, but a *direct and unambiguous disclosure* of the subject matter of Patentee's claims. In the present case, there is simply no mention in document D1 of the existence of different polymorphs for crystalline desloratadine, and certainly no teaching that either of the solid products produced in Example 1G is polymorph Form 2. Thus, in order to maintain an allegation of lack of novelty the Opponent must demonstrate, *beyond any reasonable doubt*, that polymorph Form 2 desloratadine is *always* the *inevitable result* of the process that is described within that example, no matter how that process is carried out (as noted previously the disclosure in Example 1G is not particularly detailed and so a person of skill in the art is left with a number of choices for putting the example into effect). The Opponent has certainly failed to do this.

More particularly, the Opponent has failed to repeat the disclosure that is found in Example 1G of document D1 even once, let alone to use a representative range of the numerous permitted conditions, let alone to characterise the above-mentioned two solid products (it has even failed to conduct a part of that example, e.g. to produce the intermediate product). Instead, the Opponent is simply attempting to rely on: (a) the mere use in that example of the solvent ethyl acetate (which reliance is unjustified since as will be discussed further below, ethyl acetate is a solvent whose use *may* lead to the production of the polymorph Form 2 desloratadine *provided that the crystallisation conditions are properly controlled*); and (b) an alleged similarity between the melting point of the final product of Example 1G and the melting point of polymorph Form 2 desloratadine (despite the fact that the indication of a particular melting point is entirely inconclusive for identifying a solid product as a specific polymorphic form of desloratadine, as is again discussed below).

4. The use of ethyl acetate in Example 1G does not lead to Form 2 desloratadine

As previously noted, the teaching that is found within the patent in suit provides the very first disclosure of the existence of different polymorphic forms of the antihistamine desloratadine. Moreover, it clearly discloses how to obtain crystalline polymorph Form 1 desloratadine that is essentially free of polymorph Form 2 desloratadine (as recited in granted Claim 1), and crystalline polymorph Form 2 desloratadine that is substantially free of polymorph Form 1 desloratadine (as recited in granted Claim 8). Thus, Examples 1, 2 and 3 of the patent in suit describe a number of different processes for producing polymorph Form 1 desloratadine that is essentially free of polymorph Form 2 (see e.g. column 15, lines 28-30 and column 16, lines 10-13 and 52-57 of the patent in suit describing an analysis of the Form 1 product by FTIR spectrophotometry). In addition, Examples 4 and 5 of the patent in suit describe two different processes for the production of polymorph Form 2 desloratadine that is substantially free of polymorph Form 1 (again confirmed by FTIR spectrophotometry; see e.g. column 17, lines 17-20 and 49-52 of the patent). In other words, the patent in suit provides an enabling disclosure of the production of these two different polymorphs of desloratadine, and hence of the subject matter of the claims as granted.

Considering the production of crystalline polymorph Form 2 in particular, it will be noted that the solvent ethyl acetate or di-n-butyl ether is used in the above-mentioned examples (see e.g. Example 4 at column 17, line 8, and Example 5 at column 17, lines 31-32). As the OD will recognise, this is in accordance with the teaching in the patent in suit in paragraph [0008] (see column 5, line 51 to column 6, line 23), where it is indicated that of the many different solvents that were examined for the production of a particular crystalline polymorph of desloratadine "*[o]nly ethyl acetate and di-n-butyl ether were found to produce crystalline polymorph form 2 substantially free of form 1*" and that "*[u]se of di-n-butyl ether is preferred for producing crystalline form 2 substantially free of form 1*" (see column 6, lines 20-23).

Having said this, it should nevertheless be understood that the mere involvement of one of the two solvents ethyl acetate and di-n-butyl ether *may not in fact lead to the production of polymorph Form 2 desloratadine if care is not exercised during the process of crystallisation.* Thus, as reported in the patent in suit in paragraph [0008] (see column 5, lines 51-52), it is in fact the use of "specific solvents *and experimental conditions*" which consistently produces the different crystalline polymorphs. Thus, it is entirely possible for a person of skill in the art to include one of the above-mentioned solvents in the reaction liquor and yet still not produce polymorph Form 2 desloratadine, e.g. because care has not been taken to use the specified experimental conditions during the recovery of the solid desloratadine that provide for controlled formation and growth of a specific crystalline polymorph. Indeed, an illustration of this point can readily be found in Example 1G of document D1, which (as the evidence on file

already shows) does *not* in fact lead to the production of polymorph Form 2 desloratadine substantially free of Form 1 desloratadine, despite the involvement of the solvent ethyl acetate.

Examining document D1 in a little more detail, the intermediate product of Example 1G is *just that*, an intermediate product. As a result, the example fails to specify any conditions of crystallisation that lead to the controlled formation and growth of a particular crystalline polymorph. Instead, the process which leads to the production of the intermediate product is simply a step of recovering solid material as quickly as possible by evaporating the solvent, without any regard for the type of solid, e.g. for the type of crystal, that is being formed. Of course, the absence of such a teaching is not at all surprising given that the existence of the different crystalline polymorphic forms of desloratadine had not in fact been discovered when the example was written. This absence of such a teaching is also not surprising given that the recovered intermediate product is immediately dissolved in toluene (which of course destroys any crystalline structure). In other words, there is not even any reason as to why the skilled person would examine the type of the crystals that are being formed as the intermediate product, since he immediately destroys their crystalline structure by subsequent dissolution in toluene.

In short, because the objective of the step of solvent removal is merely to obtain a solid product which can subsequently be dissolved in and crystallised from toluene, the example fails to disclose that the removal of solvent to produce the intermediate product should be carried out with care and under the specified conditions to promote a controlled formation and growth of a uniform crystalline polymorph. Instead, the solvent is simply "stripped off" as rapidly as possible by evaporation, such that the subsequent steps of dissolution of the intermediate product in toluene, and the crystallisation of the final product from that solution can begin.

Finally in this regard, Patentee observes that the conditions that are specified in Examples 4 and 5 of the patent in suit for the controlled formation and growth of the specific polymorph Form 2 of desloratadine are certainly not disclosed in Example 1G of document D1. In each of those examples, a crystalline product is allowed to develop as the resultant desloratadine solution is *cooled* to either 0°C (Example 4) or to -20°C (Example 5), thereby to precipitate the solid product, with that solid product being carefully filtered (so as to remove impurities in the mother liquor) and then dried. By way of contrast, the person of skill in the art is taught in Example 1G to "remove the solvent" so to recover the intermediate product, by which he would understand that the solvent should be evaporated off (i.e. removed using *heat*), e.g. by using a rotary evaporator (as is acknowledged by the Opponent on page 5 of its Statement of Opposition; see line 23 of Section 3). Importantly, the use of evaporation to recover a solid product in accordance with the disclosure in Example 1G of document D1 *does not lead to the production of polymorph Form 2 desloratadine*. This is clear from the evidence already on file (see the experimental annex that accompanied the submissions that Patentee filed on 8 November 2004) and from the evidence that is filed herewith. This is discussed in more detail below.

5. The intermediate product of Example 1G is not Form 2 desloratadine

The experimental evidence that Patentee submitted on 8 November 2004 clearly shows that the intermediate product of Example 1G of document D1 is *not* crystalline polymorph Form 2 desloratadine substantially free of polymorph Form 1 desloratadine. Moreover, the evidence clearly demonstrates that the intermediate product of Example 1G is also *not* polymorph

Form 1 desloratadine essentially free of polymorph Form 2 desloratadine, and is also *not* a mixture of polymorph Form 1 desloratadine and polymorph Form 2 desloratadine.

In this connection, Patentee has already provided infrared and X-ray diffraction spectra of the intermediate product according to Example 1G of document D1 (using two samples, 82071-106 and 82071-113, representing slightly different methods of solvent removal by evaporation), and compared these four spectra to the spectra that are obtained with polymorph Form 1, polymorph Form 2, and a mixture of polymorph Form 1 and polymorph Form 2 desloratadine.

Specifically, the IR spectra of the two samples 82071-106 and 82071-113 are provided in Figures 1 and 2 of the experimental annex which Patentee submitted on 8 November 2004, wherein the IR spectrum that is produced by a mixture of 93% polymorph Form 1, and 7% polymorph Form 2, is shown as the top trace. This latter spectrum (the "reference standard") contains peaks that are characteristic of polymorph Form 1 desloratadine (e.g. 3303 cm^{-1}) and of polymorph Form 2 desloratadine (e.g. 3326 cm^{-1}), as can be seen most clearly in Figure 2, wherein the relevant region of the full spectra of Figure 1 has been expanded. The presence of these peaks is of course entirely expected since the spectrum that is obtained with a *mixture* of the two polymorphic forms will contain the peaks that are found in the spectra that are obtained using each of the two polymorphic forms alone (i.e. the spectrum of the mixture represents the addition of the spectra of the individual polymorphs). Having said this, it will be readily apparent that the spectra of the two samples 82071-106 and 82071-113, which represent the intermediate product of Example 1G of document D1, do *not* contain peaks that are characteristic of the individual polymorphic Forms 1 and 2. In particular, the spectra of these two samples do not contain the characteristic peaks at 3303 cm^{-1} and at 3326 cm^{-1}.

In short, it can be concluded from the above-mentioned data that the intermediate product of Example 1G as represented by samples 82071-106 and 82071-113 is neither Form 1 desloratadine which is essentially free of Form 2 desloratadine, nor Form 2 desloratadine which is substantially free of Form 1 desloratadine, nor a mixture of these two polymorphic forms. The subject matter of Patentee's claims is therefore novel over the disclosure of the intermediate product.

A similar conclusion can be drawn from the X-ray diffraction spectra that are shown in Figures 3 and 4 of the experimental annex which was submitted by Patentee. These spectra show the peaks that are obtained with polymorph Form 1 desloratadine (see the top trace), polymorph Form 2 desloratadine (middle trace), and either sample 82071-106 (Figure 3, bottom trace) or sample 82071-113 (Figure 4 bottom trace). As the OD will readily observe, peaks which are characteristic of the individual polymorphic forms cannot be found within the spectra that are obtained with the above-mentioned samples 82071-106 and 82071-113. Thus, the intermediate product of Example 1G of document D1 as represented by these samples is not polymorph Form 1 desloratadine, is not polymorph Form 2 desloratadine, and is not a mixture of polymorph Form 1 desloratadine and polymorph Form 2 desloratadine.

In further support of this point (to the extent that further support is needed), Patentee files herewith the enclosed Figure 5, which contains the spectra that are obtained with polymorph Form 1 desloratadine, with polymorph Form 2 desloratadine, and with sample 82071-106 (as before). However, the figure also shows the spectrum that is obtained with a mixture of 70% polymorph Form 1 desloratadine and 30% polymorph Form 2 desloratadine. Thus, the fact that a mixture of polymorph Form 1 desloratadine and polymorph Form 2 desloratadine leads to a spectrum having peaks which are characteristic of the individual polymorphs when

measured alone can be readily seen. As discussed above, therefore, the absence of such characteristic peaks from the spectra that are obtained with samples 82071-106 and 82071-113 clearly indicates that the intermediate product of Example 1G of document D1 is *not* polymorph Form 1 desloratadine, is not polymorph Form 2 desloratadine, and is not a mixture of polymorph Form 1 desloratadine and polymorph Form 2 desloratadine.

To summarise: (1) the mere involvement of ethyl acetate, e.g. the presence of ethyl acetate in Example 1G of document D1, does not inevitably lead to the production of polymorph Form 2 desloratadine; (2) this is confirmed by the above-mentioned IR and X-ray data, which shows that the intermediate product of Example 1G is *not* polymorph Form 2 desloratadine (nor polymorph Form 1 desloratadine, nor a mixture of polymorph Form 1 desloratadine and polymorph Form 2 desloratadine); (3) instead of following the teaching in the patent in suit, whereby a crystalline product is allowed to develop as the desloratadine solution is cooled to 0°C or to -20°C so as to precipitate the product, which product is then carefully filtered and dried (which thereby produces crystalline polymorph Form 2 desloratadine substantially free of polymorph Form 1 desloratadine), the skilled person is simply taught by Example 1G to "remove the solvent", i.e. to strip off the solvent by evaporation. This does not lead to the production of polymorph Form 2 desloratadine substantially free of polymorph Form 1.

The subject matter of Patentee's Claims 8-13 is novel over the disclosure in document D1 of the intermediate product of Example 1G. The requirements of Article 54 EPC are satisfied.

6. The final product of Example 1G is not Form 2 desloratadine

As noted above, the Opponent has asserted that the final product of Example 1G (i.e. the product that is obtained after crystallisation from toluene) is polymorph Form 2 desloratadine. As with the Opponent's previous allegations, such an assertion is nothing more than mere speculation: the Opponent has failed to repeat Example 1G (or indeed any part of it) even once and has thus failed to obtain, let alone to characterise, the contentious final product.

As noted previously, the melting point of desloratadine as reported in the example is incapable of identifying the final product as polymorph Form 2 desloratadine. Melting point is not an accurate way of distinguishing between polymorphic forms of desloratadine (infrared spectra and X-ray diffraction data should instead be used) this being clear from the filing and discussion of document D4, in Patentee's submissions dated 8 November 2004 (see e.g. section 4.3 of Patentee's submissions). For the avoidance of doubt, document D4 is *not* being offered as evidence of the state of the art at the priority date of the patent in suit, but merely as evidence that the determination of melting point is inappropriate for distinguishing between the different polymorphic forms of crystalline desloratadine. Thus, the fact that this document may only have been published after the priority date of the patent in suit is wholly immaterial [this being stated in response to the comments by the OD in paragraph 3 of its preliminary opinion].

In light of the above, it simply cannot be asserted that the final product of Example 1G of document D1 is Form 2 desloratadine: there is simply no evidence in support of this. In this regard, and as should now be appreciated, the use of ethyl acetate in the *earlier* part of Example 1G is certainly not determinative of the identity of the final product for two important reasons. These are: (i) that the mere involvement of ethyl acetate does not in fact mean that the intermediate product of Example 1G, which is then dissolved in and crystallised from toluene so as to produce the final product, is polymorph Form 2 desloratadine (as has been discussed above); and (ii) that *whatever the form of desloratadine that is produced as the*

intermediate product, it cannot simply be assumed that this particular crystalline form of desloratadine will be carried through into the final product.

To expand on this second reason in a little more detail, the OD will note that according to the disclosure in Example 1G of document D1, the intermediate product that is produced in that example is *dissolved in toluene*, and then crystallised *from that solvent* (and not from ethyl acetate). Thus, *as a result of this step of dissolving the intermediate product in toluene, any crystal structure that was previously formed will now have been destroyed*, thereby negating the impact of the earlier reaction steps (including *inter alia* the use of ethyl acetate), in relation to the form of the crystalline product that is produced. In other words, whatever the crystalline structure of the intermediate product of Example 1G, this is certainly not carried through into the final product of the example, because that crystal structure is immediately destroyed (and then a different crystal structure is formed when the solid is then crystallised from a different solvent, i.e. toluene). In other words, the crystal form of desloratadine that is produced as the final product of Example 1G is entirely *in*dependent of the crystal structure of the intermediate product, but is instead *dependent on the solvent that is used for the recrystallisation* (which solvent is toluene, not ethyl acetate).

Now as noted elsewhere herein, it has not been shown that toluene leads to the production of polymorph Form 2 desloratadine (indeed, it is only the solvents ethyl acetate and di-n-butyl ether that have been shown to produce polymorph Form 2 desloratadine substantially free of Form 1 under specified conditions; see e.g. column 6, lines 20-23 of the patent in suit). Thus, it simply cannot be assumed that the identity of the final product of Example 1G of document D1 is Form 2 desloratadine as the Opponent asserts.

Moreover, Patentee has conducted additional experimental tests, which demonstrate that the crystallisation of desloratadine from toluene consistently results in a mixture of approximately 80% of polymorph Form 1 desloratadine and 20% of polymorph Form 2 desloratadine. Specifically, two different mixtures of desloratadine with different ratios of polymorph Form 1 to polymorph Form 2 were subjected to dissolution in and crystallization from toluene, in accordance with the disclosure in Example 1G of document D1. The data are summarized in the following table, with the different polymorphic forms being detected by IR.

Experiment Number	Form 1 : Form 2 before crystallisation	Form 1 : Form 2 after crystallisation
84752-53-30	>95 : <5	80 : 20
84752-55	70 : 30	77 : 23

The data indicate that crystallisation from toluene results in a mixture of approximately 80% polymorph Form 1 and approximately 20% polymorph Form 2 desloratadine, *irrespective of the fact that the ratio of polymorph Form 1 desloratadine to polymorph Form 2 desloratadine within the starting samples was different in these experiments*. Thus, these experiments suggest that the final product of Example 1G of document D1 that results from crystallisation from toluene is (at best for the Opponent) 80% polymorph Form 1 desloratadine and 20% polymorph Form 2 desloratadine, which therefore fails to impugn the novelty of Patentee's granted Claims 8-13 (or any other claims of the patent in suit). The Opponent has not provided any evidence to the contrary and the requirements of Article 54 EPC are once again satisfied.

7. Summary

In light of the evidence that Patentee has submitted in this case and the analysis that has been provided above, it is clear that the subject matter that is defined by Patentee's claims is novel over the disclosure in the state of the art. Neither the intermediate product nor the final product of Example 1G of document D1 is polymorph Form 1 desloratadine essentially free of polymorph Form 2 desloratadine, or polymorph Form 2 desloratadine substantially free of polymorph Form 1 desloratadine. The requirements of Article 54 EPC are therefore fulfilled. The patent should be maintained as granted.

8. Auxiliary Claim Request

In the event that the OD forms an intention not to maintain the patent in the form in which it was granted (i.e. in the form of Patentee's current Main Request), Patentee hereby requests that the patent should be maintained on the basis of the Auxiliary Claim Request that is filed herewith, together with an appropriately amended description.

In addition, Patentee requests the opportunity at the Oral Proceedings to make amendments to the Main Request, or to the Auxiliary Claim Request, in order that it might deal with any minor deficiencies that the OD considers to be present within an otherwise allowable set of claims.

Yours faithfully

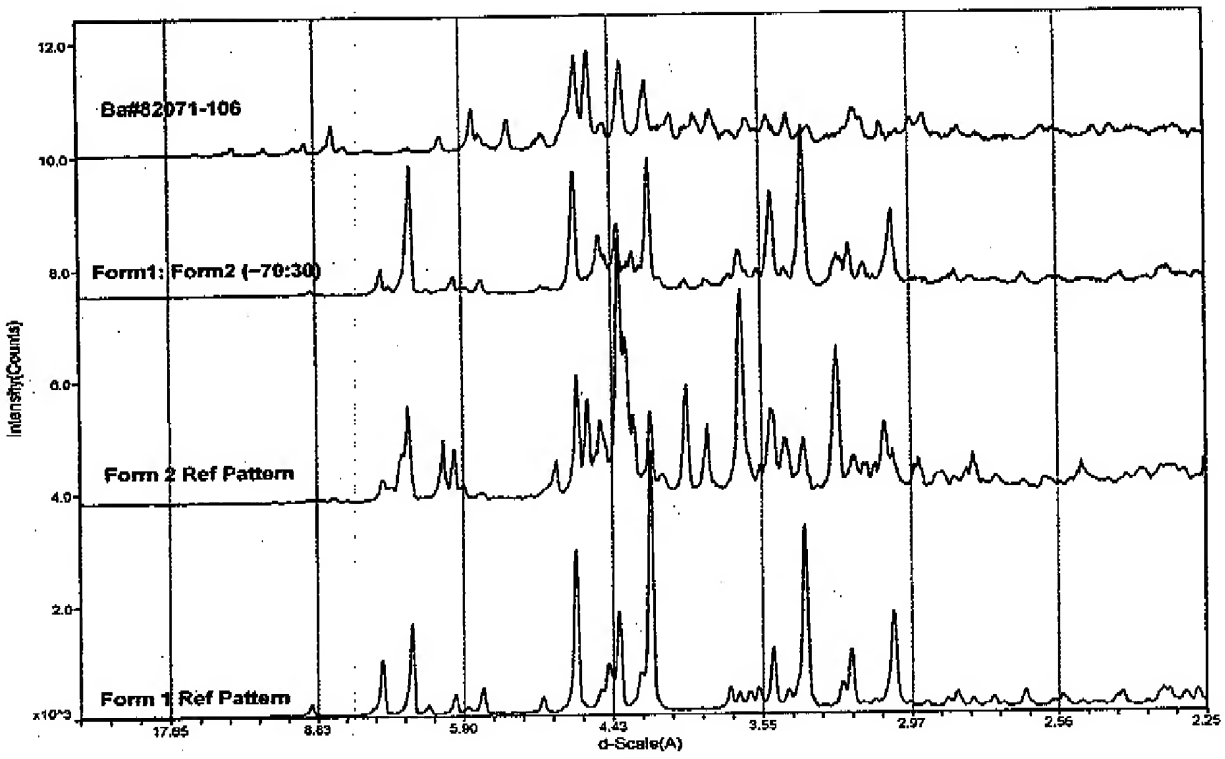
H.Adams.

Harvey V. J. Adams
MATHYS & SQUIRE

Enc: *Curriculum vitae* of each technical expert
Figure 5
Auxiliary Claim Request

/fm

Figure 5


Ba#82071-106
Form1: Form2 (~70:30)
Form 2 Ref Pattern
Form 1 Ref Pattern
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3.55
2.97
2.56
2.25
d-Scale(A)